ORIGINAL ARTICLE

Prevalence of depression and anxiety in patients with cystic fibrosis and parent caregivers: results of The International Depression Epidemiological Study across nine countries

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ABSTRACT

Background Individuals with chronic diseases and parent caregivers are at increased risk for symptoms of depression and anxiety. Prevalence of psychological symptoms was evaluated in adolescents and adults with cystic fibrosis (CF) and parent caregivers across nine countries.

Methods Patients with CF, ages 12 years and older, and caregivers of children with CF, birth to18 years of age, completed measures of depression and anxiety across 154 CF centres in Europe and the USA. Psychological symptoms were compared across countries using χ^2. Logistic regression examined extent of comorbid symptoms, predictors of depression and anxiety, and concordance between parent and adolescent symptomatology.

Results Psychological symptoms were reported by 6088 patients with CF and 4102 parents. Elevated symptoms of *depression* were found in 10% of adolescents, 19% of adults, 37% of mothers and 31% of fathers. Elevations in *anxiety* were found in 22% of adolescents, 32% of adults, 48% of mothers and 36% of fathers. Overall, elevations were 2–3 times those of community samples. Participants reporting elevated anxiety were more likely to report depression (ORs: adolescents=14.97, adults=13.64, mothers=15.52, fathers=9.20). Significant differences in reports of depression and anxiety were found by patient age and parent respondent. Concordance between 1122 parent–teen dyads indicated that adolescents whose parents reported depression were more likely to be elevated on depression (OR=2.32). Similarly, adolescents whose parents reported anxiety were more likely to score in the elevated range on the anxiety measure (OR=2.22).

Conclusions Symptoms of depression and anxiety were elevated in both patients with CF and parents across several European countries and the USA. Annual screening of psychological symptoms is recommended for both patients and parents.

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Key messages

What is the key question?
▶ What is the prevalence of symptoms of depression and anxiety in adolescents and adults with cystic fibrosis (CF) and parents of children with CF, ages from birth to 17 years, in an international study across 9 countries using standardised screening measures?

What is the bottom line?
▶ Significant elevations in symptoms of depression and anxiety were found among patients and parent caregivers across countries, suggesting that screening for symptoms of depression and anxiety should be performed annually and addressed systematically.

Why read on?
▶ This is the largest international screening study performed in a chronic respiratory disease and has led to the creation of an international guidelines committee to formulate recommendations leading to a change in medical practice.

INTRODUCTION

Meta-analyses and systematic reviews have indicated that children and adults with chronic diseases, as well as parent caregivers, are at increased risk for depression and anxiety.[1–3] Cystic fibrosis (CF) is the most common genetic, life-limiting chronic disease among Caucasian populations and requires a treatment regimen that takes between 2 and 4 h per day.[4] Patients have genetic mutations that affect the CF transmembrane conductance regulator protein, leading to thick mucus secretions, repeated infections and progressive failure of most organ systems (e.g., lungs, pancreas, digestive, reproductive).[5] Although recent advances in diagnosis and treatment have led to increases in lifespan, CF continues to be one of the most difficult chronic conditions to manage.[6]

Studies evaluating depression and anxiety in patients with CF have generally found a high prevalence of psychological distress. Rates of depression in children and adolescents have ranged from 9% to 29%, using different methods of assessment (ICD-10 diagnoses, Children's

Depression Inventory).[7] For adults with CF, rates of depression have ranged from 13% to 30%[8][9] and rates of anxiety from 30% to 33%.[8][10] Among parent caregivers, elevations in psychological distress have also been found, with depression ranging from 20% to 35%.[7][11][12] Overall, psychological symptoms appear to be higher in this population than community samples[13]; however, these studies have been limited by small sample sizes and different screening or diagnostic tools, which have made interpretation of the results difficult. Additionally, the majority of studies have only assessed symptoms of depression but not anxiety.

Psychological distress in patients with CF has been associated with a number of negative consequences and health outcomes, including worse adherence,[7][14] worse pulmonary function,[10][15] increased hospitalisations and healthcare costs,[16] and decreased health-related quality of life.[8][9] A recent study[16] compared adolescents with CF who had been diagnosed with a depressive disorder with a matched sample of non-depressed teens with CF, and found that those who were depressed were three times more likely to be hospitalised for a pulmonary exacerbation, and incurred much higher healthcare costs over 2 years (US $280 000 for the depressed group vs. US$60 116 for the non-depressed group). Given both the wide range of prevalence estimates for patients with CF and their caregivers, and the negative impact these symptoms have on disease management and functioning, The International Depression Epidemiological Study group aimed to screen depression and anxiety in several European countries and the USA. Two screening measures were used to assess these symptoms in both adolescents and adults with CF and parent caregivers. Predictors of psychological symptoms, both demographic and medical, were also identified, comorbidity of depression and anxiety was estimated and concordance between parents and children was evaluated.

METHODS
Procedure
This study was conducted at 154 CF centres in nine countries: Belgium, Germany, Italy, Spain, Sweden, The Netherlands, Turkey, the UK and the USA. The protocol was developed by a consortium of investigators over a 2-year period, with discussions each year in Europe and the USA to refine the protocol. Investigators then applied for funding from their country's respective patient with CF or research foundations, with 7 out of 9 countries obtaining small grants. Although the procedures and data collection were standardised to a great extent, some countries chose to use only one screening tool for depression (i.e., Hospital Anxiety and Depression Scale; HADS) because it was widely used in their country[17] (note that the HADS is not used in the USA). Five out of the nine countries used both the HADS and the Center for Epidemiologic Studies-Depression Scale (CES-D). Screening was initiated in patients aged 12 years through adulthood and in parents of children from birth to 18 years of age. Study protocols were approved by national and local ethics committees or institutional review boards at all CF centres.

Staff members approached participants at routine, stable, clinic visits. After completion of consent/assent, patients or parents completed a basic demographic questionnaire in addition to the screening measures. When both parents were present, they completed the symptom measures independently. Depression and anxiety screening measures were scored immediately by trained staff members to identify clinically elevated scores; referrals were provided if necessary. Completion of the

measures took approximately 15 min. Medical data were collected through chart review.

Participants
Across nine countries, 1286 adolescents (mean age=14.84 years, SD=1.69) and 4739 adults (mean age=28.87 years, SD=9.5) with CF were screened. Inclusion criteria were: (1) confirmed diagnosis of CF, (2) age within specified range and (3) screening during stable clinic visit. Patients who had received a solid organ transplant were excluded. Additionally, 3127 mothers and 975 fathers of younger children reported on their own symptoms. Descriptive demographic and medical data are presented in table 1.

Measures
Demographic and medical characteristics
Parents and young adults completed a Background Information Form assessing parent and child/adolescent's age, gender and education. Information about pharmacological and psychological treatment of depression and anxiety was also collected. Indicators of physical health status in the past 6 months were recorded from medical charts (FEV_1% predicted, height, weight, haemoptysis/pneumothorax, intravenous antibiotics, and listed for transplant).

Hospital Anxiety and Depression Scale
The HADS is a 14-item instrument; seven questions measure depression and seven measure anxiety.[18] It has extensive reliability and validity data, and was designed specifically for patients with chronic medical conditions (i.e., removal of somatic items). Respondents indicated the severity of each symptom on a 4-point rating scale (0–3) over the past week. Maximum score is 21; participants were categorised using established cut-off scores (mild=8–10, moderate=11–15, severe=≥16). Validated translations were used in Europe.

Center for Epidemiologic Studies-Depression scale
The CES-D is a well-established self-report measure of depressive symptomatology for community samples.[19] It has 20 items measuring symptoms of depression that reflect diagnostic criteria on the DSM-IV and has correlated well with diagnostic interviews. Items are rated on a 4-point scale from 0 to 3, with higher scores indicating more depressive symptoms. The maximum score is 60, with ≥16=elevated. Valid translations were used in Europe.

Statistical analyses
Missing data
Missing data occurred because some countries did not collect data on both screening measures or because participants did not provide a response. Countries that did not collect information on a particular measure were excluded from the analyses that involved that measure or question. The amount of missing data from participants who did not provide a response ranged from 0% to 7%, depending on the measure. Because few participant responses were missing, this was unlikely to significantly bias the results, and we opted to use complete cases in all analyses.[20]

Nesting of participants within country
Participants were nested within 9 countries. In analyses that pooled data across countries, this nesting was accounted for by including country as a fixed effect (i.e., different intercept for each country) in the models. We chose to use a fixed effect approach because we did not have specific hypotheses about

Table 1 Participant characteristics by respondent

	Respondent							
	Adolescent	Adult	OR or η^2	p Value	Mothers*	Fathers*	OR or η^2	p Value
Sample size	1286	4739			3127	975		
Age, mean (SD), years	14.84 (1.69)	28.87 (9.54)	0.32	<0.001	8.90 (5.08)	8.52 (5.14)	<0.01	0.040
Female (%)	669 (53)	2271 (48)	1.14	0.044	1558 (50)	460 (47)	1.14	0.075
BMI, mean (SD)	19.54 (3.11)	21.87 (3.54)	0.07	<0.001	17.47 (2.99)	17.28 (2.92)	<0.01	0.102
FEV_1 percent predicted, mean (SD)	83.78 (23.44)	62.32 (24.51)	0.12	<0.01	89.23 (21.55)	90.74 (22.13)	<0.01	0.112
Haemoptysis or pneumothorax in 6 months (%)	35 (3)	657 (14)	0.21	<0.001	37 (1)	9 (1)	0.98	0.969
Currently on intravenous antibiotics (%)	156 (12)	733 (16)	0.50	<0.001	299 (10)	118 (12)	1.22	0.146
Listed for transplant (%)	7 (1)	243 (5)	0.09	<0.001	12 (0.4)	1 (0.1)	–	–
Currently on psychiatric medication for depression/anxiety (%)	44 (4)	466 (10)	0.29	<0.001	59 (2)	9 (0.9)	1.95	0.231
Currently receiving psychotherapy for depression/anxiety (%)	70 (6)	379 (8)	0.63	0.001	103 (3)	19 (2)	1.23	0.526
Positive scores (%)					*Caregivers*			
HADS-D	60 (5)	609 (13)	0.30	<0.001	618 (20)	173 (18)	1.15	0.142
CES-D	87 (19)	488 (29)	0.53	<0.001	1057 (34)	240 (25)	1.58	<0.001
Either HADS-D or CES-D	130 (10)	913 (19)	0.39	<0.001	1165 (37)	305 (31)	1.34	<0.001
HADS-A	281 (22)	1503 (32)	0.60	<0.001	1496 (48)	343 (36)	1.70	<0.001

*Characteristics of younger patients whose parents completed the screening. The amount of variability across strata was estimated using η^2 for continuous variables. ORs comparing younger with older participants and Mothers with Fathers, were used to index the size of the differences between the strata.
HADS, Hospital Anxiety and Depression Scale; CES-D, Center for Epidemiologic Studies-Depression Scale; BMI, body mass index.

difference between countries, did not want to make assumptions about countries not included in the sample and because the limited number of countries posed challenges for alternative approaches (e.g., multilevel modelling).[21]

Demographic and prevalence estimates

Prevalence estimates were based on published cut scores,[18 19] and then divided into two groups according to 'caseness': (1) non-case (below cut-off) and (2) case (mild-severe symptoms). Demographic and prevalence estimates were analysed using two stratifications. Estimates were first stratified by a respondent to test differences by respondent age (<18 vs. ≥18 years) and by mothers vs. fathers. Differences between ages and respondents on dichotomous variables were tested using a Generalised Linear Model (GLIM) with a binomial error distribution and a logit link function. The size of the difference between strata was quantified using ORs comparing younger with older respondents, and mothers with fathers. Similar GLIMs were used for all analyses of dichotomous outcomes that pooled data across countries. Differences on continuous variables were estimated using a General Linear Model, and η^2 was used to quantify the size of the differences. Estimates were also stratified by country to test for variability among countries. For dichotomous variables, variability across strata was tested using a χ^2 test, and the amount of variability was estimated using Cramér's V(φ_c). For continuous items, the variability was tested using a General Linear Model, and η^2 was used to quantify the amount of variability.

Comorbidity and concordance

Theoretically, a great deal of evidence suggests that anxiety often precedes depression,[22] therefore, a GLIM was used to assess the odds of reporting elevations in depression given respondents' reports of anxiety. Concordance between 1130 parent–adolescent dyads was also evaluated using a GLIM. The model evaluated the odds that adolescents would report symptoms above the cut-off given that their parents also reported symptoms above the cut-off; these analyses were conducted separately for depression and anxiety scores.

Predictors of depression and anxiety

To identify predictors of depression and anxiety, data were pooled across countries and stratified by participant age (<18 vs. ≥18 years) and respondent (mother vs. father). Potential predictors included the 9 variables collected on the *Demographic and Medical Characteristics* form and are listed in tables 1 and 2. Each predictor was evaluated separately using a GLIM that accounted for country of origin.

All analyses were run using SAS V.9.3.

RESULTS

Demographics

Demographic and health information for patients and caregivers are presented in table 1 and are reported by country in table 2. On average, patients were in their mid-20s, about half were female, body mass index (BMI) was in the normal range and lung function indicated moderate disease severity. Significant variability was found across countries on age, gender, BMI and FEV_1% predicted, however, these effects were small. Across countries, variability was also found in the predictors of psychological distress: haemoptysis/pneumothorax (2%–32%), currently on intravenous antibiotics (5%–19%), listed for transplant (2%–12%), and pharmacological/psychological treatment of depression or anxiety (3%–23%).

Prevalence of symptoms of depression

Rates of depression varied depending on age and screening tool: adolescents 5%–19%, adults 13%–29%, mothers 20%–34% and fathers 18%–25% (table 1 and figure 1). Analyses by country indicated that overall, 11% of patients were elevated on the HADS-D (range 8%–15%) and 27% of patients were elevated on the CES-D (range 20%–31%) (table 2). Because the

Table 2 Participant characteristics by country

	Countries										φ_c or η^2	p Value
	BE	DE	IT	NL	ES	SE	TR	UK	US	TOTAL		
Sample size	426	663	741	515	275	167	52	2042	1207	6088		
Age, mean (SD), years	25.55 (10.09)	23.53 (9.22)	24.52 (9.38)	27.50 (11.39)	25.82 (7.81)	26.84 (12.16)	12.86 (5.97)	26.98 (10.18)	25.40 (10.86)	25.76 (10.31)	0.03	<0.001
Female	201 (47)	316 (48)	383 (52)	239 (47)	119 (43)	81 (49)	32 (63)	993 (49)	527 (53)	2963 (49)	0.06	0.014
BMI, mean (SD)	20.58 (3.34)	19.93 (2.98)	20.52 (3.05)	21.33 (3.15)	21.36 (3.82)	21.84 (3.33)	18.71 (3.99)	22.10 (3.78)	21.70 (3.83)	21.34 (3.60)	0.05	<0.001
FEV₁ percent predicted, mean (SD)	72.34 (24.55)	67.22 (25.60)	73.83 (26.97)	66.25 (26.12)	64.67 (26.12)	74.66 (26.89)	71.90 (26.26)	62.55 (24.49)	67.89 (26.08)	66.99 (25.84)	0.03	<0.001
Haemoptysis/pneumothorax last 6 months	31 (7)	27 (4)	–	101 (24)	32 (12)	4 (4)	1 (2)	279 (14)	223 (32)	698 (14)	0.17	<0.001
Currently on intravenous antibiotics	72 (17)	–	–	56 (11)	14 (5)	19 (19)	8 (18)	129 (6)	182 (17)	461 (11)	0.16	<0.001
Received an organ transplant	10 (2)	18 (3)	–	27 (6)	20 (7)	2 (2)	1 (2)	43 (2)	131 (12)	252 (5)	0.18	<0.001
Currently on psychiatric medication for depression/anxiety	40 (9)	14 (2)	–	16 (3)	17 (6)	8 (5)	3 (7)	158 (8)	257 (23)	513 (10)	0.24	<0.001
Currently receiving psychotherapy for depression/anxiety	22 (5)	53 (9)	–	17 (3)	13 (5)	11 (12)	3 (7)	145 (7)	190 (18)	401 (9)	0.17	<0.001
HADS depression											0.08	<0.001
Non-case (0–7)	361 (85)	599 (90)	683 (86)	466 (90)	244 (89)	154 (92)	37 (71)	1810 (89)	1052 (91)	5361 (89)		
Case (8–21)	65 (15)	63 (10)	103 (14)	49 (10)	31 (11)	13 (8)	15 (29)	232 (11)	100 (9)	671 (11)		
CES-D depression	106 (28)	–	–	102 (20)	75 (31)	–	16 (52)	–	259 (29)	558 (27)	0.11	<0.001
Either HADS or CES-D	122 (29)	63 (10)	103 (14)	114 (22)	83 (30)	13 (8)	30 (58)	232 (11)	287 (25)	1047 (17)	0.11	<0.001
HADS Anxiety											0.14	<0.001
Non-case (0–7)	286 (67)	526 (79)	486 (66)	443 (86)	204 (74)	129 (77)	36 (69)	1374 (67)	755 (66)	4239 (70)		
Case (8–21)	140 (33)	136 (21)	255 (34)	72 (14)	71 (26)	38 (23)	16 (31)	668 (34)	397 (35)	1793 (30)		

Notes: unless otherwise noted, values represent No. (%), only participants with non-missing values were included in the calculation of the percentages.
Shading shows data from Turkey which were not used in the logistic regression. The amount of variability across strata was estimated using Cramér's V(φ_c) for categorical variables and η^2 for continuous variables.
BE, Belgium; DE, Germany; ES, Spain; HADS, Hospital Anxiety and Depression Scale; IT, Italy; NL, Netherlands; SE, Sweden; TR, Turkey; CES-D, Center for Epidemiologic Studies-Depression Scale; BMI, body mass index; '–' indicates data was not collected.
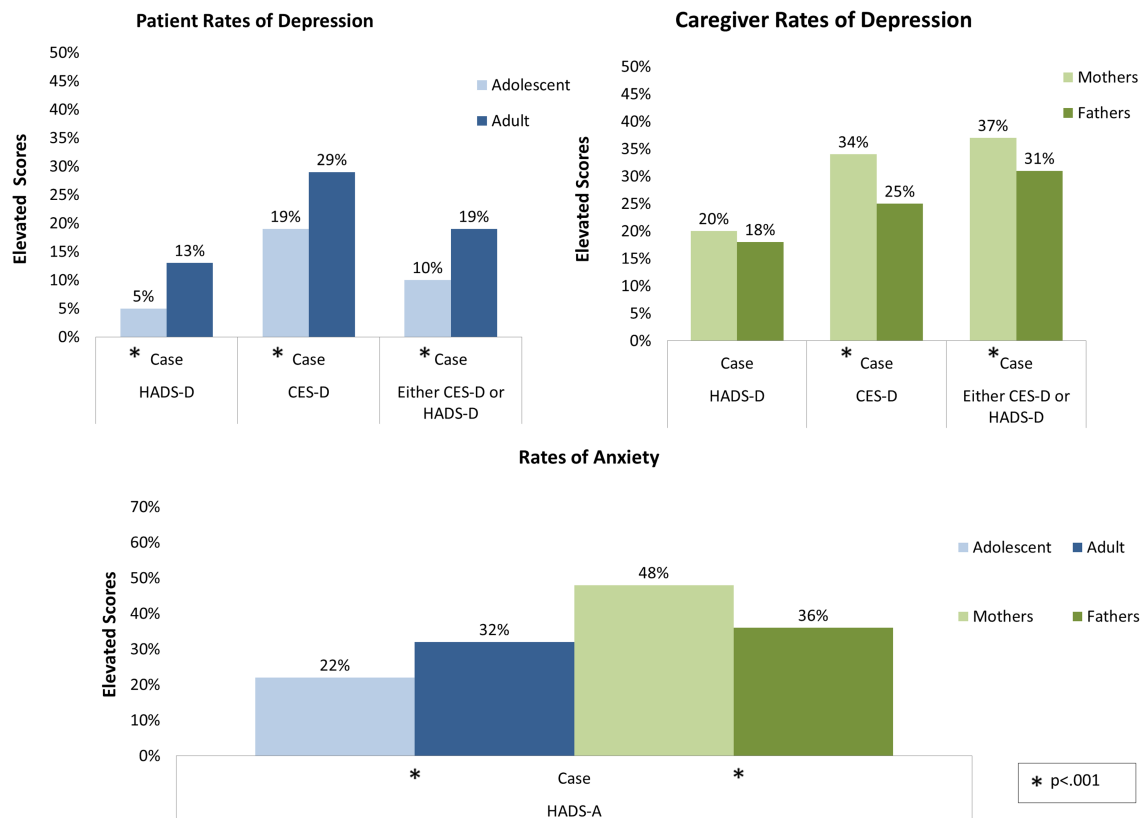
Figure 1 Rates of depression and anxiety by respondent.

sample size for Turkey was small and the availability of standard medications for CF is limited, their estimates were not included in the ranges above (i.e., Turkey: depression on the HADS-D=29%, CES-D=52%). Statistically significant differences were found by age (see table 1), with adolescents reporting fewer symptoms of depression than adults (19% vs. 29% on the CES-D; p<0.001). Mothers reported significantly more depressive symptoms than fathers on the CES-D (34% vs. 25%; p<0.001), but not on the HADS-D (20% vs. 18%).

For the countries that administered both the CES-D and HADS-D to patients, significant differences in prevalence rates were found between measures. Comparing the CES-D with the HADS-D, the OR for adolescents was 4.45 (p<0.001) and the OR for adults was 2.90 (p<0.001). For mothers, the OR was 1.88 (p <0.001) and for fathers it was 1.09 (p=0.650).

Prevalence of symptoms of anxiety

Symptoms of anxiety were prevalent in patients and parents: adolescents 22%, adults 32%, mothers 48% and fathers 36% (see table 1 and figure 1). Analyses by country indicated high rates of anxiety among patients (mean 30%), with moderate variability across countries (14%–35%; Turkey falls within this range). Statistically significant differences were found by age, with 22% of adolescents vs. 32% of adults (p<0.001) reporting elevations in anxiety above the cut-off score (see table 1, figure 1). Mothers also reported significantly more symptoms of anxiety than fathers (48% vs. 36%, p<0.001).

Comorbidity between depression and anxiety

In terms of both the theory[22] and the higher rates of anxiety observed across both patients and parents, bidirectional relationships between anxiety and depression were examined by calculating the odds that those with elevated anxiety would also score in the elevated range for depression. Adolescents reporting elevated anxiety had odds of reporting depression that were 14.97 times higher than adolescents not reporting anxiety; 6% of adolescents reported elevations on both. Adults reporting anxiety were 13.64 times more likely to report elevated depression than those not elevated on anxiety; 14% of adults reported elevations on both. Mothers reporting elevated anxiety were 15.52 times more likely to report elevations in depression; 31% reported elevations on both. For fathers with elevated anxiety, they were 9.20 times more likely to report elevated depression; 21% reported elevations on both. All effect sizes were large.

Concordance between parent and adolescent depression and anxiety

For the 1122 dyads with both parent and teen reports, adolescents were 2.39 times more likely be above the cut-off for depression if at least one of their parents had elevated symptoms and they were 2.22 times more likely to be above the cut-off for anxiety if their parent was also elevated.

Predictors of depression and anxiety

Predictors of depression and anxiety were identified using univariate logistic regressions (see table 3). For adolescents, the following characteristics were associated with elevated symptoms of depression on the CES-D or HADS-D: being female, an episode of haemoptysis/pneumothorax in past 6 months, taking psychiatric medication for depression or anxiety and receiving psychotherapy for depression or anxiety. Characteristics associated with elevated anxiety were: being female, recently on IV antibiotics and receiving psychotherapy.

Table 3 Univariate logistic regression results predicting depression or anxiety by respondent

	Respondent							
	Adolescent		Adult		Mother		Father	
	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value	Odds ratio (95% CI)	p Value
HADS or CESD depression								
Age, years	1.01 (0.89 to 1.13)	0.963	1.03 (1.02 to 1.04)	<0.001	0.99 (0.98 to 1.01)	0.315	0.99 (0.96 to 1.01)	0.304
Female	1.77 (1.17 to 2.66)	0.007	1.09 (0.94 to 1.26)	0.277	0.95 (0.81 to 1.10)	0.472	0.93 (0.70 to 1.23)	0.610
BMI	1.03 (0.98 to 1.10)	0.261	1.01 (0.99 to 1.03)	0.266	1.01 (0.98 to 1.03)	0.696	1.03 (0.99 to 1.09)	0.173
FEV$_1$ percent predicted*	0.98 (0.90 to 1.06)	0.621	0.90 (0.88 to 0.93)	<0.001	1.00 (0.96 to 1.04)	0.971	0.95 (0.88 to 1.03)	0.198
Haemoptysis/pneumothorax in last 6 months	3.82 (1.63 to 8.95)	0.002	1.62 (1.33 to 1.98)	<0.001	0.96 (0.47 to 1.97)	0.920	1.29 (0.31 to 5.34)	0.723
Intravenous antibiotics	1.74 (0.94 to 3.21)	0.076	1.65 (1.33 to 2.04)	<0.001	1.53 (1.17 to 2.01)	0.002	1.72 (1.12 to 2.63)	0.013
Received an organ transplant†	–	–	1.39 (1.03 to 1.87)	0.030	1.10 (0.31 to 3.85)	0.880	–	–
Currently on psychiatric medication for depression/anxiety	3.96 (1.94 to 8.08)	0.003	3.56 (2.86 to 4.42)	<0.001	1.51 (0.88 to 2.61)	0.137	0.68 (0.14 to 3.33)	0.631
Currently receiving psychotherapy for depression/anxiety	6.54 (3.56 to 12.01)	<0.001	3.21 (2.54 to 4.06)	<0.001	1.88 (1.25 to 2.83)	0.002	0.52 (0.15 to 1.84)	0.313
HADS anxiety								
Age, years	0.99 (0.91 to 1.07)	0.790	1.02 (1.01 to 1.03)	<0.001	0.98 (0.97 to 1.00)	0.034	0.98 (0.95 to 1.00)	0.082
Female	1.63 (1.23 to 2.15)	<0.001	1.66 (1.46 to 1.88)	<0.001	0.94 (0.81 to 1.09)	0.404	0.83 (0.63 to 1.09)	0.173
BMI	0.99 (0.95 to 1.04)	0.793	1.03 (1.01 to 1.05)	0.003	0.99 (0.97 to 1.02)	0.504	0.98 (0.94 to 1.03)	0.530
FEV$_1$ percent predicted*	1.01 (0.95 to 1.07)	0.765	0.96 (0.93 to 0.98)	0.002	0.99 (0.95 to 1.03)	0.541	0.99 (0.91 to 1.06)	0.706
Haemoptysis/pneumothorax in last 6 months	2.03 (0.99 to 4.14)	0.053	1.38 (1.15 to 1.65)	<0.001	1.32 (0.67 to 2.58)	0.424	0.82 (0.20 to 3.44)	0.790
Intravenous antibiotics	1.73 (1.13 to 2.66)	0.012	1.14 (0.94 to 1.37)	0.185	1.52 (1.16 to 1.98)	0.002	1.10 (0.71 to 1.71)	0.674
Received an organ transplant†	–	–	1.34 (1.01 to 1.77)	0.039	0.91 (0.29 to 2.90)	0.879	–	–
Currently on psychiatric medication for depression/anxiety	1.91 (1.00 to 3.68)	0.051	3.37 (2.74 to 4.14)	<0.001	0.97 (0.57 to 1.65)	0.919	0.64 (0.16 to 2.63)	0.537
Currently receiving psychotherapy for depression/anxiety	2.77 (1.65 to 4.62)	<0.001	4.22 (3.37 to 5.30)	<0.001	2.02 (1.32 to 3.09)	<0.001	2.03 (0.79 to 5.17)	0.139

*ORs are for a 10% change in FEV$_1$ percent predicted.
†Variable was not included in the model for 12-year-olds to 18-year-olds due to small number of cases.
HADS, Hospital Anxiety and Depression Scale; CES-D, Center for Epidemiologic Studies-Depression Scale; BMI, body mass index.

For adults, depression was associated with: older age, lower FEV$_1$% predicted, haemoptysis or pneumothorax in the past 6 months, recently on intravenous antibiotics, listed for transplant, taking psychiatric medications and receiving psychotherapy. Characteristics associated with elevated symptoms of anxiety were: older age, being female, lower BMI, lower FEV$_1$, haemoptysis/pneumothorax, listed for transplant, taking psychiatric medications and receiving psychotherapy.

For mothers, child characteristics associated with depression were: recently on intravenous antibiotics and receiving psychotherapy. Elevated anxiety was associated with: younger age, recent intravenous antibiotics and receiving psychotherapy. For fathers, only one child medical variable was associated with depression: recent intravenous antibiotics.

DISCUSSION

This is the largest psychological screening study conducted in a chronic respiratory disease, with data collected from both European countries and the USA. Results across nine countries revealed high rates of depression and anxiety in adolescents and adults with CF, as well as parent caregivers. Elevated depression was reported by 17% of patients across countries, regardless of which screening tool was used—a rate two times that reported in community populations (9.2%).[23] Similarly, although there are fewer large-scale studies of caregivers, 37% of mothers and 31% of fathers reported clinically elevated depression, which is three times the rate in community samples.[23][24] Rates of anxiety were also elevated in patients and caregivers, with 30% of patients and 36%–48% of parents above the clinical cut-off. These rates are two to three times those reported in community samples.[25–27]

Given these high rates of psychological symptoms and their documented effects on disease management, including clinic attendance and adherence to prescribed treatments,[7][16][28] annual screening of depression and anxiety for adolescents and adults with CF and parent caregivers is warranted. This conclusion is consistent with several international guidelines, which recommend regular screening for adolescents and adults with chronic conditions—particularly if these symptoms impact daily functioning and management of the disease.[29–32] For example, the American Diabetes Association recommends screening of psychological symptoms at 'regular clinical encounters' and when there is 'concern about poor management'.[32] To date, however, there is no guideline recommendation for screening parent caregivers.

As found in prior studies, comorbidity of anxious and depressive symptoms within individuals was high, suggesting that elevations in anxiety confer a heightened risk for depression. Analyses of parent-adolescent dyads showed that depression or anxiety in either parent doubled the risk that the adolescent would report elevated psychological distress. This well-established comorbidity between parents and adolescents provides a second rationale for screening parent caregivers. Identification and treatment of parental psychological distress

may both prevent adolescents with CF from developing psychological symptoms, and when detected in parents, prompt the medical team to provide referrals for mental health services to the family.

We used two well-established screening measures of depression, and in countries that used both (i.e., 5 out of 9 countries), comparisons indicated that the HADS-D underestimated symptoms of depression by a factor of two. Although when the study protocol was being developed, the HADS was considered well established and widely used, more recent evidence has clearly shown that this screening tool has significant problems, including lack of sensitivity, underestimation of symptoms and a three-factor, rather than two-factor structure, and is not recommended for screening.[33–35] Additionally, it was chosen because it did not contain somatic items (e.g., fatigue). A posthoc analysis of the rank ordering of depressive symptoms on the CES-D in our patient sample, showed that no somatic items were ranked among the top three. In fact, the symptoms with the highest severity ratings focused on hopefulness about the future, self-esteem and extent of happiness. Further, a comparison of items on the HADS-D and CES-D revealed that many of the diagnostic criteria in the DSM-IV/V were not represented on the HADS-D (e.g., cognitive impairment, lack of energy). Instead, the vast majority of items on the HADS-D measured anhedonia (72%), which represents lack of enjoyment and pleasure in activities.[36] By contrast, the CES-D included items representing the full spectrum of depressive symptoms underlying this construct.

Several risk factors were associated with elevated depression and anxiety. Older age and female sex, worse disease severity, as indicated by lower lung function or BMI, and recent *changes in health status* (past 6 months), such as haemoptysis or prescription of intravenous antibiotics. Treatments for psychological distress (with medication or psychotherapy) were the highest risk factors. For parents, recent course of intravenous antibiotics and current treatment for a psychological disorder were associated with greater symptomatology.

Limitations and future directions

Although the demographic and health information from the three largest samples in this study (UK, USA and Germany) appeared quite similar to data in their respective national registries,[11 15] it is possible that this sample is not representative of the larger international population. In screening studies, those who are experiencing the most severe symptoms are *less* likely to attend regular clinic visits or give informed consent for participation in research, and thus, these prevalence rates may be an *underestimate* of the population.[37] This study was also limited by the cross-sectional nature of the data collection. Prospective, longitudinal studies are needed to determine: which health variables *predict* increases in psychological symptoms and what health *consequences* follow identification of elevated scores (e.g., decreased adherence, increases in pulmonary exacerbations, increases in healthcare use and cost, decreases in health-related quality of life).

These results highlight the importance of measuring and treating mental health issues in patients and families coping with serious, chronic illnesses. Our findings, in conjunction with other smaller studies, have led to the formation of an international committee, sponsored by both the European Cystic Fibrosis Society and the Cystic Fibrosis Foundation, to develop guidelines on mental health screening and treatment in CF. As advocated by other national guidelines committees, we have recommended annual screening of depression and anxiety in adolescents and adults with CF, and parent caregivers using the PHQ-9 and GAD-7.[23 30–32 38 39] Our goals are to implement these screening recommendations using the unique structure of accredited and recognised CF centres in Europe and the USA and to take advantage of the existing data registries in Europe, the UK and the USA to better understand the relationships between psychological distress and health outcomes.

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